

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.,
Petitioner,
v.

CALIFORNIA INSTITUTE OF TECHNOLOGY,
Patent Owner

Case No. IPR2024-01178

U.S. Patent No. 10,770,170 B2

DECLARATION OF KEVIN STRUHL, PH.D.

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. EXPERT QUALIFICATIONS AND CREDENTIALS.....	1
III. BASIS FOR OPINIONS, AND MATERIALS REVIEWED.....	3
IV. UNDERSTANDING OF THE LAW	9
A. A Person Having Ordinary Skill in the Relevant Field During the Relevant Time	9
B. Claim Interpretation in <i>Inter Partes</i> Review.....	11
C. Anticipation	12
D. Obviousness.....	12
E. Priority Date	14
V. BACKGROUND ON RELEVANT TECHNOLOGY.....	14
A. Technology	15
B. The '170 Patent and the Challenged Claims	18
C. The '170 Patent's Prosecution History	24
D. Saxonov Provisional and Priority Date	25
E. Overview of Saxonov	30
F. Overview of Silverbrook.....	40
G. Overview of Maltezos	40
H. Overview of Oh	41
I. Overview of Nakamura	41
J. Overview of Larson.....	41
VI. CLAIM CONSTRUCTION	47
VII. GROUNDS OF CHALLENGE.....	48
A. Ground 1 (Claims 1-9, 20): Obviousness over Saxonov	48

B.	Ground 2 (Claims 10-12): Obviousness Over Saxonov and Nakamura	61
C.	Ground 3 (Claims 13-16): Obvious Over Saxonov and Silverbrook	61
D.	Ground 4 (Claims 17, 19): Obviousness Over Saxonov and Maltezos	62
E.	Ground 5 (Claim 18): Obviousness Over Saxonov, Maltezos, and Further in View of Oh	62
F.	Ground 6 (Claims 1-9, 20): Obviousness Over Saxonov and Larson	63
G.	Grounds 7-10 (Claims 10-19): Obviousness Over Saxonov and Larson and Further in View of Nakamura, Silverbrook, Maltezos, and/or Oh	66
VIII.	DECLARATION	66

DECLARATION OF DR. KEVIN STRUHL

I, Kevin Struhl, declare as follows:

I. INTRODUCTION

1. I am making this Declaration at the request of California Institute of Technology (“Patent Owner”) in the matter of IPR2024-01178, a petition for *Inter Partes* Review of U.S. Patent No. 10,770,170 (“the ’170 Patent”).

2. I am being compensated for my work in these matters at a rate of \$1200 per hour for my professional consulting services. I am also reimbursed for my reasonable expenses incurred in connection with my work in this proceeding. My compensation is not in any way contingent upon the outcome of this *Inter Partes* Review. I have no interest in the outcome of this proceeding or any related litigation.

II. EXPERT QUALIFICATIONS AND CREDENTIALS

3. My qualifications for presenting the opinions in this Declaration are set forth below and in my *curriculum vitae*, a copy of which is provided as EX2002.

4. I earned Bachelor’s and Master’s degrees in biology from the Massachusetts Institute of Technology (MIT) in 1974. I earned a Ph.D. in biochemistry from Stanford University in 1979. I have been a professor of Biological Chemistry and Molecular Pharmacology at Harvard University since

1982.

5. In addition to teaching courses in molecular biology and biochemistry while serving on the faculty at Harvard University for nearly 42 years, I actively researched various topics combining genetic, molecular, biochemical, genomic, and evolutionary approaches to study many aspects of gene regulation and yeast, and the processes of cellular transformation and formation of cancer stem cells. In the course of conducting my research, I have used multiplex polymerase chain reaction (PCR). Indeed, I started using multiplex PCR twenty years ago, which is before real-time PCR machines existed.

6. I have also accrued substantial industry experience. For example, I served as a member of the advisory board for Pharmagenics Inc. from 1991 to 1997. I was also a member of the advisory board for Scriptgen Inc. from 1993 to 2000. I also was a member of the advisory board for Sangamo Inc. from 1999 to 2015. I am currently a member of the advisory board for UTR Therapeutics.

7. I have authored or co-authored over three hundred publications in the fields of biochemistry and molecular biology.

8. Additionally, I was one of the founding editors of *Current Protocols in Molecular Biology*, the manual which publishes the standards for experimental design, methods, and analyses in all areas of molecular biology. I have authored procedures for quantitative PCR for this journal.

9. I have been qualified as a PCR and/or DNA sequencing expert in multiple litigations, including in proceedings before U.S. District Courts, the International Trade Commission, and Patent Trial and Appeal Board.

III. BASIS FOR OPINIONS, AND MATERIALS REVIEWED

10. The opinions set forth in my Declaration are based on my personal knowledge gained from my education, on my personal experience, and on the review of the documents and information described in this Declaration.

11. In preparation of this Declaration, I have considered:

- Exhibit 1001: U.S. Patent No. 10,770,170 (“’170 Patent”);
- Exhibit 1002: Declaration of Carl A. Batt, Ph.D.;
- Exhibit 1003: Joint Claim Construction Statement, filed on June 18, 2024, Dkt No. 65, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23- cv-06360, N.D. Cal.;
- Exhibit 1004: U.S. Patent Application Publication No. US 2013/0040841 A1 “Saxonov”;
- Exhibit 1005: Information Disclosure Statement noting Saxonov from Prosecution File History of U.S. Patent No. 10,068,051 filed on March 23, 2018;
- Exhibit 1006: Notice of Allowance from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018;

- Exhibit 1007: U.S. Patent Provisional Application No. 61/510,013
(filed July 20, 2011) (Serge Saxonov, Simant Dube, John F. Regan, applicants) (“Saxonov Provisional”);
- Exhibit 1009: U.S. Patent Application Publication No. US 2011/0312704 A1 “Silverbrook”;
- Exhibit 1010: U.S. Patent Application Publication No. US 2008/0003649 A1 “Maltezos”;
- Exhibit 1011: U.S. Patent Application Publication No. US 2010/0311070 A1 “Oh”;
- Exhibit 1012: U.S. Patent No. 10,770,170 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal.;
- Exhibit 1013: Synbio Technologies, Precision and Accuracy with TaqMan Probes, <https://synbio-tech.com/precision-and-accuracy-with-taqman-probes/>;
- Exhibit 1014: Pamela M. Holland, et al., “Detection of specific polymerase chain reaction product by utilizing the 5’ → 3’ exonuclease activity of *Thermus aquaticus* DNA polymerase,”

Proc. Natl. Acad. Sci. USA, Vol. 88, pp. 7276-7280, August 1991

Biochemistry “TaqMan Paper”;

- Exhibit 1015: Information Disclosure Statement from Prosecution
File History of U.S. Patent No. 10,770,170 filed on March 22,
2018;
- Exhibit 1016: Information Disclosure Statement from Prosecution
File History of U.S. Patent No. 11,827,921 filed on March 25,
2021;
- Exhibit 1017: U.S. Patent Application Publication No. US
2011/0250597 A1 “Larson”;
- Exhibit 1019: Plaintiff and Counter-Defendant ChromaCode Inc.’s
Amended Patent L.R. 3-5 Disclosure of Preliminary Invalidity
Contentions; Patent L.R. 3-4 Document Production, served on
February 29, 2024, *ChromaCode, Inc. v. Bio-Rad Laboratories et
al.*, Case No. 5:23-cv-04823, N.D. Cal.;
- Exhibit 1020: Simant Dube, et al., “Mathematical Analysis of
Copy Number Variation in a DNA Sample Using Digital PCR on a
Nanofluidic Device,” PLoS One, Volume 3, Issue 8, August 2008
“Dube Paper”;
- Exhibit 1021: U.S. Patent No. 9,487,822 “Dube patent”;

- Exhibit 1022: U.S. Patent No. 9,366,632 “Link”;
- Exhibit 1023: Federal Judicial Caseload Statistics (2023), at <https://www.uscourts.gov/statistics-reports/analysis-reports/federaljudicial-caseload-statistics>;
- Exhibit 1024: Civil Minutes - General, filed on December 7, 2023, Dkt No. 34, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 2:23-cv-08417, C.D. Cal.;
- Exhibit 1025: U.S. Patent Application Publication No. US 2011/0160288 A1 “Nakamura”;
- Exhibit 1026: U.S. Patent Application Publication No. US 2010/0173394 A1 “Colston”;
- Exhibit 1027: Joint Stipulation and Order Regarding Filing of Second Amended Complaint and Amended Case Schedule, filed on March 27, 2024, Dkt No. 53, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360, N.D. Cal.;
- Exhibit 1028: Amended Complaint for Patent Infringement of U.S. Patent Nos. 10,068,051 and 10,770,170, filed on October 13, 2023, Dkt No. 12, *ChromaCode, Inc. et al. v. Bio-Rad Laboratories*, Case No. 2:23-cv-08417, C.D. Cal.;

- Exhibit 1029: U.S. Patent No. 8,730,479 “Application No. 13/341,678” (as issued);
- Exhibit 1030: Office Action Summary from Prosecution File History of U.S. Patent No. 10,770,170 filed on July 22, 2019;
- Exhibit 1031: Amendment and Response to Final Office Action and Request for Continued Examination from Prosecution File History of U.S. Patent No. 10,770,170 filed on January 21, 2020;
- Exhibit 1032: Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,770,170 filed on April 26, 2018;
- Exhibit 1033: References Cited by Applicant and Considered by Examiner from Prosecution File History of U.S. Patent No. 10,770,170 filed on February 24, 2019;
- Exhibit 1036: Nucleic Acids, <https://www.genome.gov/genetics-glossary/Nucleic-Acids>, updated July 7, 2024;
- Exhibit 1037: Introduction of Molecular Beacons, https://molecularbeacons.org/MB_introduction.html;
- Exhibit 1038: Shivaprasad H. Sathyanarayana and Lauren M. Wainman, “Chapter 2, Laboratory approaches in molecular

pathology: the polymerase chain reaction,” Diagnostic Molecular Pathology, 2024;

- Exhibit 2002: *Curriculum Vitae* of Kevin Struhl, Ph.D.;
- Exhibit 2003: File History of U.S. Patent No. 10,770,170;
- Exhibit 2004: U.S. Provisional Application No. 61/507,082;
- Exhibit 2005: Patent Scheduling Order dated March 8, 2024, Dkt No. 47, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360 (N.D. Cal.);
- Exhibit 2006: Petitioner’s Amended Invalidity Contentions, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360 (N.D. Cal.)
- Exhibit 2007: Comparison of Saxonov and Saxonov Provisional
- Exhibit 2008: Appendix A to Bio-Rad’s Amended Invalidity Contentions;
- Exhibit 2009: Appendix C to Bio-Rad’s Amended Invalidity Contentions;
- Exhibit 2010: Docket, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360 (N.D. Cal.);

- Exhibit 2011: Plaintiff’s Opening Claim Construction Brief, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360 (N.D. Cal.); and
- Exhibit 2012: Reply Claim Construction Brief, *ChromaCode, Inc. v. Bio-Rad Laboratories et al.*, Case No. 5:23-cv-06360 (N.D. Cal.).

IV. **UNDERSTANDING OF THE LAW**

12. I am not an attorney. In preparing and expressing my opinions and considering the subject matter of the ’170 Patent, I am relying on certain basic legal principles that have been explained to me. These principles are discussed below.

A. **A Person Having Ordinary Skill in the Relevant Field During the Relevant Time**

13. I understand that the disclosures of patents and prior art references are to be viewed from the perspective of a mythical person of ordinary skill in the relevant field (sometimes referred to by lawyers as “the relevant art”) at the relevant timeframe (a “POSA”). I understand that, for purposes of this IPR proceeding, I should interpret the term POSA as referring to a mythical person to whom an expert in the relevant field could have assigned a routine task with reasonable confidence that the task would be successfully carried out.

14. I have been asked to provide my opinion regarding the “level of ordinary skill in the art” at the time of the invention, which I understand is on or before February 3, 2012.

15. I understand that the hypothetical person of ordinary skill in the art is considered to have the normal skills and knowledge of a person in a certain technical field. I understand that factors that may be considered in determining the level of ordinary skill in the art include: (1) the education level of the inventor; (2) the types of problems encountered in the art; (3) the prior art solutions to those problems; (4) rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the education level of active workers in the field. I also understand that “the person of ordinary skill” is a hypothetical person who is presumed to be aware of the universe of available prior art.

16. I also understand the level of ordinary skill in the art can be evidenced by the prior art. Accordingly, I have also considered the prior art discussed herein in determining the level of ordinary skill in the art.

17. Petitioner asserts that a POSA relevant to the '170 Patent as of February 3, 2012 would have a Ph.D. in molecular biology, genetics, biochemistry, or a related discipline, with at least a year of experience in quantitative and/or digital PCR and fluorescence-based analyte detection. Alternatively, the Petitioner asserts that a POSA would have been someone with greater relevant experience

sufficient to compensate for having less relevant formal education. The Petitioner states that a POSA would have “understood” several technologies and techniques which are enumerated in the Petition.

18. I understand that, for purposes of this IPR proceeding, PO does not contest Petitioner’s description of qualifications for a POSA. Therefore, I adopt Petitioner’s definition of a POSA for purposes of this declaration.

19. I would qualify as at least a POSA at all relevant times for purposes of this proceeding, including at least as early as the priority date of the ’170 Patent. I have a Ph.D. in biochemistry with at least a year of experience in quantitative and/or digital PCR and fluorescence-based analyte detection.

B. Claim Interpretation in *Inter Partes* Review

20. I understand that the first step in determining the validity of a claim is for the claim to be properly construed. I understand that “claim construction” is the process of determining a patent claim’s meaning. I also understand that the proper construction of a claim term is the meaning that a POSA would have given to that term during the relevant timeframe.

21. For purposes of *Inter Partes Review*, I understand that the Board applies the *Phillips* standard, under which claims are to be given their ordinary and customary meaning as understood by a POSA at the time the application was filed. I understand that this analysis is performed by primarily looking to the patent’s

claims, specification (including drawings), and prosecution history (the “intrinsic” evidence). I understand that if the claim is unclear in view of the intrinsic evidence, then outside (“extrinsic”) evidence also may be considered.

C. Anticipation

22. I understand that a patent claim is unpatentable as anticipated if a POSA during the relevant timeframe would have understood a single prior art reference to disclose an embodiment that expressly or inherently teaches every limitation contained in the claim. The disclosure in a reference does not have to be in the same words as the claim, but all of the requirements of the claim must be described in enough detail, or necessarily inherent in an embodiment disclosed in the reference, to enable a POSA looking at the reference to practice the claimed invention.

D. Obviousness

23. I understand that a patent claim also, or alternatively, is unpatentable if it would have been obvious to a POSA during the relevant timeframe. I understand that the following factors must be evaluated to determine whether the claimed subject matter was obvious: (1) the scope and content of the prior art; (2) the difference or differences, if any, between the subject matter defined by the claim of the patent under consideration and what is disclosed in the prior art; (3) the level of ordinary skill in the relevant field at the time of the patent’s earliest

priority date or, possibly, at an earlier time; and (4) so-called “objective evidence of non-obviousness.” However, I understand that, for the present, I can ignore both the possibility that obviousness is to be determined at a date earlier than the patent’s earliest priority date and the possibility that Patent Owner will submit objective evidence of non-obviousness.

24. I understand that prior art references can be combined to support a finding that a claim is unpatentable for obviousness when there was an apparent reason for one of ordinary skill in the art, at the time of the invention, to combine the references and that such apparent reasons include: (A) identifying a teaching, suggestion, or motivation to combine prior art references; (B) combining prior art methods according to known methods to yield predictable results; (C) substituting one known element for another to obtain predictable results; (D) using a known technique to improve a similar device in the same way; (E) applying a known technique to a known device ready for improvement to yield predictable results; (F) trying a small number of identified, predictable potential solutions, with a reasonable expectation of success; and (G) identifying that known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the relevant field.

25. Moreover, I understand that so-called “objective indicia of non-obviousness” (also known as “secondary considerations”) like the following can be considered when assessing obviousness: (1) commercial success; (2) long-felt but unresolved needs; (3) copying of the invention by others in the field; (4) initial expressions of disbelief by experts in the field; (5) failure of others to solve the problem that the inventor solved; and (6) unexpected results. I also understand that evidence of objective indicia of non-obviousness must be commensurate in scope with the claimed subject matter.

E. Priority Date

26. I understand that to be entitled a priority date of an earlier-filed application, the earlier-filed application must provide support for the invention claimed in the later-filed application as required by the “written description” requirements of 35 U.S.C. § 112. I understand that an adequate written description requires showing that the inventor was in possession of the invention at the time of the patent application’s filing.

27. I understand that in order to show the possession of the claimed invention, a POSA must discern the claimed invention with all of its limitations based on disclosure of the patent or patent application at issue, including the originally filed claims, specifications, and/or the drawings.

V. BACKGROUND ON RELEVANT TECHNOLOGY

A. Technology

28. A variety of techniques, including polymerase chain reaction (PCR), have been developed to detect a target polynucleotide analyte, such as a particular genetic sequence, within a biological sample. *See* EX1001, 11:7-12, 11:46-12:27; EX1017(Larson), ¶¶3-6 (“Assays have been developed that rely on analyzing nucleic acid molecules from bodily fluids for the presence of mutations...The advent of PCR and real-time PCR methodologies has greatly improved the analysis of nucleic acids from both throughput and quantitative perspectives.”).

29. Caltech’s innovations described and claimed in the ’170 Patent and its priority applications addressed a long-standing problem in the field: namely, as the number of analytes in a biological sample increases, it quickly becomes more complicated to identify the analytes. EX1001, 1:31-43. The term “multiplexing” refers to a broad class of techniques for detecting multiple analytes in a biological sample. EX1001, 1:31-43; *see also* EX1017(Larson), ¶45. Early assays used PCR to amplify (create copies of) each of the target polynucleotide analytes, and often involved gel electrophoresis to separate the various PCR products that distinguished the analytes. EX1001, 1:31-43.

30. A subsequent multiplex PCR approach uses “probes” to bind to target analytes and fluoresce with different colorimetric label (fluorophores) corresponding to the different analytes, with results being detected with

appropriate optical channels. EX1001, 11:13-45, 8:29-58; *see also* EX1017(Larson), ¶¶4-5 (“qPCR reactions are monitored either using a variety of highly sequence specific fluorescent probe technologies[.]”). For example, a probe for a particular genetic sequence is designed to be complementary to that sequence, and they bind via hybridization. *See* EX1002(Batt Decl.), ¶¶36-37, 39-40, 42. For example, a probe is designed to be complementary to a particular genetic sequence, and the probe and sequence bind via hybridization. EX1001, 11:13-44. The fluorophore emits light only if the probe has bound its target within the sample. EX1001, 9:15-28, 11:13-44. A TaqMan probe is a particular type of probe that functions by releasing a fluorescent reporter molecule upon probe binding to its target DNA sequence and subsequent PCR amplification, wherein the 5’ exonuclease activity of the extending DNA polymerase cleaves the probe, separating the fluorescent reporter from a quencher molecule, resulting in an increase in fluorescence. EX1001, 10:27-29 (“‘TAQMAN probe’ generally refer[s] to hydrolysis probes used to detect the presence of an analyte in a polynucleotide amplification assay.”); EX1017(Larson), ¶47; *see also* EX1002(Batt Decl.), ¶¶36-37, 39-40, 42. Such techniques to detect a target polynucleotide analyte in a biological sample were generally known, and commercially available TAQMAN probes were, and still are, commonly used to detect specific genetic sequences in this manner.

31. For example, a probe with a blue fluorophore binds analyte A and its light is observed in a blue channel; and a probe with a red fluorophore binds analyte B and its light is observed in a red channel. EX1001, 11:47-12:27. Of course, increasing the numbers of probe types (each with distinct fluorophore color) and channels (one per color) increases the number detectable analytes. EX1001, 12:30-36. However, this has the limitation of the number of distinct colorimetric probes and optical channels that could be assayed simultaneously. *Id.*

32. Some multiplexing techniques use probes with colorimetric labels (fluorophores) of the same color. *See* EX1017(Larson), ¶5, ¶47; EX1001, 8:29-40. Here, color alone does not distinguish the analytes from one another: light in the channel means an analyte is present, but does not identify *which* analyte is present. *Id.* Analytes that are indistinguishable from one another in a given assay may be referred to as “degenerate.” *See* EX1001, 16:27-37. Some techniques (*e.g.*, Larson) tried to avoid this problem by (i) highly diluting the sample, (ii) physically dividing the diluted sample into droplets, (iii) observing the intensity of light from each droplet, and (iv) drawing conclusions about the analytes based on that intensity. *See, e.g.*, EX1017(Larson), ¶6. For example, probes with the same color could be designed to fluoresce at different intensities, so as to identify the analyte using the intensity. *See* EX1017(Larson), ¶12.

33. When a dilute sample is divided into droplets, different droplets may contain different numbers of unique analyte molecules. EX1017(Larson), ¶6. The “Poisson distribution” describes the statistics of how many molecules the droplets contain. *See id.* In the “limiting dilution” regime, the majority of droplets contain zero analyte molecules, fewer droplets contain exactly one analyte molecule, even fewer contain exactly two analyte molecules, still fewer contain exactly three analyte molecules, and so on. EX1017(Larson), ¶6. At terminal dilution, the sample is sufficiently diluted that the Poisson distribution basically guarantees that almost all droplets are either empty or contain only a single analyte molecule, with droplets rarely containing multiple analyte molecules. *Id.* At terminal dilution, to best avoid droplets containing multiple analyte molecules, most droplets are empty, which wastes material and time.

34. The ’170 Patent refers to analytes that are indistinguishable from one another in a given assay as being “degenerate.” EX1001, 16:28-31. At the time the ’170 Patent and its priority applications were filed, a significant need remained for inexpensive, material-efficient, and time-efficient multiplexing that could non-degenerately identify a higher number of targets within a given sample, without the need to add another optical channel corresponding to each additional analyte. EX1001, 1:31-43, 8:41-58.

B. The ’170 Patent and the Challenged Claims

35. The '170 Patent inventors conceived of a solution – described and claimed in the '170 Patent and its priority applications – that enables non-degenerate detection of at least five polynucleotide analytes, in a sample, in any combination of presence or absence. The application that issued as the '170 Patent was filed on March 7, 2018 as a continuation of Application No. 14/451,876, which is a continuation of Application No. 13/756,760, filed February 1, 2013, now U.S. Patent No. 8,838,394. EX1001, §§(22), (63). The '170 Patent claims priority to Provisional Application Nos. 61/594,480, filed February 3, 2012 and 61/703,093, filed September 19, 2012. EX1001, §(60).

36. The '170 Patent inventors recognized that in traditional multi-channel methods such as described above, “the number of detectable analytes is equal to the number of spectrally resolvable fluorophores. Therefore, the number of analytes may only be increased by increasing the number of spectrally resolvable fluorophores.” *Id.*, 12:30-36. The inventors developed a technique to non-degenerately identify analytes in a sample, using *fewer* fluorophores than the number of analytes. *Id.*, 8:41-62. Such scheme is distinctive from prior multi-channel techniques or terminal dilution-based techniques described above. *Id.*; *supra* §V.A. Instead, “each analyte to be detected is encoded as a value in each of two components of a signal (*e.g.*, intensity and wavelength).” *Id.*, 8:62-9:1. These components are cumulatively measured for the sample, and the “presence or

absence of an analyte may then be determined based on the values used to encode the presence of the analyte (i.e., those values in the coding scheme).” *Id.*, 9:38-44.

37. Table 3 of the ’170 Patent, reproduced below, describes an example in which seven analytes (A-G), plus control, are encoded using combinations of four fluorophores (fewer fluorophores than analytes):

TABLE 3

Encoding of eight analytes (including control) with four colors and up to four colors per analyte.				
	Blue	Green	Yellow	Red
Ctrl. (p)	1	0	0	0
A	1	0	0	1
B	1	0	1	0
C	1	1	0	0
D	1	0	1	1
E	1	1	0	1
F	1	1	1	0
G	1	1	1	1

EX1001(’170 Patent), 13:45-58.

38. As the ’170 Patent explains, in Table 3,

The presence of the control and analyte A is indicated by a result of 2001. The presence of the control and analyte G is indicated by a result of 2111. These results express the cumulative intensity of the signal in each color. For example, the result 2111 has a 2× signal intensity in the

blue channel, while the result 1000 has only a $1\times$ signal intensity in the blue channel.

Id., 13:64-14:3.

39. While these example results are for a single analyte, the '170 Patent also explains how the inventive coding method of Table 3 may be used to detect ***combinations*** of different analytes in a single sample volume. For example, the following excerpt from Table 4 demonstrates that the cumulative signal intensity from the combination of analytes A-F in a single sample volume is different, and measurably distinguishable from, that from the combination of analytes A-G in a single sample volume:

7	3	3	3	pABCDEF
8	4	4	4	pABCDEFGG

EX1001, 15:41-42.

40. The '170 Patent inventors recognized that in some circumstances, a result may be degenerate “because it can indicate more than one possibility in terms of the presence or absence of an analyte. For example, with reference to Table 4, result 5233 is degenerate because it can be decoded as either pADFG or pBDEG.” *Id.*, 16:30-33. The inventors solved this problem by reducing or eliminating degeneracy from the coding scheme, “thereby increasing the confidence with which an analyte is detected.” EX1001, 16:38-40. The '170

Patent describes different ways to eliminate degeneracy, such as encoding individual analyte states using intensity levels separated by integer $\log_2$ intensity values (1, 2, 4, 8, 16, etc.) such that every possible combination of analytes has a unique cumulative intensity. *Id.*, 21:39-23:19.

41. One example method of eliminating degeneracy according to the '170 Patent encodes the individual analyte states using intensity levels that are separated by integer $\log_2$ differences. *Id.* This design is non-degenerate because for N analytes, there are 2^N states, and with each analyte uniquely encoded by a $\log_2$ encoding intensity value (1,2,4,8,16, etc.). The cumulative sums of analyte intensities for any combinatorial state using this $\log_2$ encoding method produce a unique cumulative intensity value for each state. This is because any N digit combinatorial state can be represented as a binary number with N digits. The presence or absence of eight different analytes in an assay can be encoded using a binary representation, such as (00100110). In this system, each analyte is assigned an intensity based on its presence and its binary position. For example, the first position corresponds to $2^0 = 1$, the second is $2^1 = 2$, the third is $2^2 = 4$, and so on. The base-10 equivalent of the binary number represents the cumulative intensity signal, with each value being unique due to the distinct binary representation of each combinatorial state. This ensures that every possible combination of analytes

has a unique cumulative intensity, allowing for precise detection and differentiation. EX1001, 23:1-19.

42. The '170 Patent claims are directed to the innovations allowing detection of “any unique combination of presence or absence of at least five polynucleotide analytes in a plurality of droplets.” *Id.*, 65:30-67:10. For example, claim 1 of the '170 Patent (sole independent claim) recites:

1. A method of unambiguously detecting any unique combination of presence or absence of at least five polynucleotide analytes in a plurality of droplets, the method comprising:

(a) providing a sample comprising, or potentially comprising, at least one of said at least five polynucleotide analytes;

(b) forming a mixture of said sample and at least five hybridization probes, wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores;

(c) partitioning said mixture into said plurality of droplets;

(d) exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes is present in said plurality of droplets, wherein said one or more signals

comprise at least one signal generated by excitement of said at least one fluorophore;

(e) measuring said one or more signals to generate a cumulative intensity measurement, wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample; and

(f) determining whether each of said least five polynucleotide analytes is present, in any unique combination of presence or absence, based on said cumulative intensity measurement,

wherein the method does not require any step of immobilization of said at least five polynucleotide analytes or mass spectrometry.

EX1001('170 Patent), 65:30-61.

C. The '170 Patent's Prosecution History

43. I understand the Examiner of the '170 Patent indicated that the application's priority applications "do not disclose the independent claim limitation of partitioning the mixture into a plurality of droplets," and accorded claims 1-20 the benefit date of February 1, 2013. EX2003, 1050.

44. I understand that the Examiner of the '170 Patent allowed the application on the basis that "[t]he claims recite the new and non-obvious limitation of determining a unique presence and absence pattern of at least five

polynucleotides in a sample using a cumulative intensity value of fluorophores and without using immobilization or mass spectrometry.” EX2003, 2117-2118. I agree with the Examiner’s assessment, for at least the reasons that I will explain in the sections which follow.

D. Saxonov Provisional and Priority Date

45. U.S. Patent Application Publication No. 61/510,013 to Saxonov et al. (“Saxonov Provisional”) is a provisional patent application to which Saxonov claims priority. However, Saxonov Provisional fails to disclose the entire subject matter of Saxonov on which Petitioner relies.

46. For example, FIGS. 1-8A and 8B of Saxonov generally correspond to, and are carried over from, FIGS. 1-8 of the Saxonov Provisional, with certain differences. However, FIGS. 9 and 10 of Saxonov are ***absent*** in the Saxonov Provisional. Nor does any disclosure in the Saxonov Provisional, as understood by a POSA, support or disclose the subject matter relied on by Petitioner from these figures. *See* EX2007, 3, 16-17.

47. As another example, ¶¶2-16, 19-36, 38-53, 45-68, and 72-75 of Saxonov generally correspond to page 1, line 10 through page 20, line 22 of the Saxonov Provisional. *Id.*; *see also* EX2007. However, ¶¶17, 18, 37, 44, 69-71, and 76-80 of Saxonov contain significant new subject matter which is ***not found in, or supported by***, the Saxonov Provisional. *Id.*; *see also* EX2007.

48. The grounds rely upon this *newly added* subject matter for the challenged claims, for example as shown below for Ground 1, claim 1:

Claim 1 limitation	Petitioner's Citation to subject matter in Saxonov (EX1004) not carried forward from Saxonov Provisional (EX1007)	Location in Petition of this citation to Saxonov
(a) providing a sample comprising, or potentially comprising, at least one of at said at least five polynucleotide analytes;	¶¶17, 77	29
(b) forming a mixture of said sample and at least five hybridization probes,	FIG. 9, ¶77	32-33
wherein each of said at least five hybridization probes further comprises at least one fluorophore and at most four fluorophores;	FIGS. 9, 10, ¶¶76-79	34

Claim 1 limitation	Petitioner's Citation to subject matter in Saxonov (EX1004) not carried forward from Saxonov Provisional (EX1007)	Location in Petition of this citation to Saxonov
(c) partitioning said mixture into said plurality of droplets;	¶78	36
(d) exciting said at least one fluorophore to generate one or more signals if one or more of said at least five polynucleotide analytes is present in said plurality of droplets, wherein said one or more signals comprise at least one signal generated by excitement of said at least one fluorophore;	¶37	37

Claim 1 limitation	Petitioner's Citation to subject matter in Saxonov (EX1004) not carried forward from Saxonov Provisional (EX1007)	Location in Petition of this citation to Saxonov
(e) measuring said one or more signals to generate a cumulative intensity measurement,	FIG. 10, ¶¶76-78	39
wherein said cumulative intensity measurement corresponds to the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample; and	FIGS. 9, 10, ¶¶17, 18, 76-79	41

Claim 1 limitation	Petitioner's Citation to subject matter in Saxonov (EX1004) not carried forward from Saxonov Provisional (EX1007)	Location in Petition of this citation to Saxonov
(f) determining whether each of said [at] least five polynucleotide analytes is present, in any unique combination of presence or absence, based on said cumulative intensity measurement,	N/A	N/A
wherein the method does not require any step of immobilization of said at least five polynucleotide analytes or mass spectrometry.	N/A	N/A

49. In short, it is my opinion that Saxonov's FIGS. 9 and 10 and ¶¶17, 18, 37, and 76-80 relied upon in Petitioner's grounds for unpatentability of numerous claims, are **not** carried over from the Saxonov Provisional and are unsupported by the Saxonov Provisional. I understand that Saxonov's FIGS. 9 and 10 and ¶¶17, 18, 37, and 76-80 therefore are **not** prior art to the '170 Patent, and that these

sections are entitled only to Saxonov's *non-provisional* filing date of July 12, 2012, which was *after* the '170 patent's earliest priority date (February 3, 2012).

50. Saxonov also claims priority to another provisional, U.S. 61/507,082, filed July 12, 2011. EX1004, §(60). However, Petitioner does not indicate any reliance upon the priority date of that provisional. Instead, Petitioner cites only to the Saxonov Provisional, which as explained above does not disclose subject matter upon which the Petition's grounds rely.

E. Overview of Saxonov

51. U.S. Patent Application Publication No. 2013/0040841 to Saxonov et al. ("Saxonov") was filed on July 12, 2012, and issued on February 14, 2013. EX1004(Saxonov), §§(22), (43).

52. Saxonov is directed to "performing a digital assay with multiplexed detection of two or more distinct targets in the same optical channel."

EX1004(Saxonov), Abstract. Regarding "digital assays," Saxonov explains:

Digital assays generally rely on the ability to detect the presence or activity of individual copies of an analyte in a sample. In an exemplary digital assay, a sample is separated into a set of partitions, generally of equal volume, with each containing, on average, less than about one copy of the analyte. If the copies of the analyte are distributed randomly among the partitions, some

partitions should contain no copies, others only one copy, and, if the number of partitions is large enough, still others should contain two copies, three copies, and even higher numbers of copies. The probability of finding exactly 0, 1, 2, 3, or more copies in a partition, based on a given average concentration of analyte in the partitions, is described by a Poisson distribution.

EX1004(Saxonov), ¶3.

53. This portion of Saxonov teaches that in a standard digital assay, most droplets (partitions) are empty, fewer droplets contain exactly one analyte, even fewer contain exactly two analytes, and even fewer contain exactly three analytes; this is consistent with the limiting dilution regime discussed above in §V.A. As described previously, in the limiting dilution regime, the sample is sufficiently diluted that the Poisson distribution basically guarantees that the majority of droplets contain zero analyte molecules. A lower number of droplets contain exactly one analyte molecule, an even lower number contain exactly two analyte molecules, an even lower number contain exactly three analyte molecules, and so on.

54. According to Saxonov, “[d]igital assays frequently rely on amplification of a nucleic acid target in partitions to enable detection of a single copy of an analyte,” and such “[a]mplification may be conducted via the

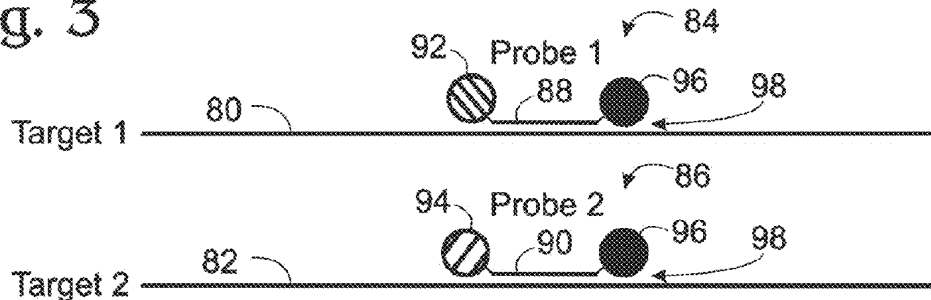
polymerase chain reaction (PCR).” EX1004(Saxonov), ¶5. Saxonov states that “[a]mplification of the target can be detected optically from a fluorescent probe included in the reaction,” and that “the probe can include a dye that provides a fluorescence signal indicating whether or not the target has been amplified.” *Id.* So, Saxonov clearly uses the term “nucleic acid target” to refer to a genetic sequence that it is desired to amplify, and then detect using the digital assay using a fluorescent probe, similarly as discussed above in §V.A.

55. Like others, Saxonov tried to multiplex: “[a] new approach is needed to increase the multiplex levels of digital assays.” EX1004(Saxonov), ¶7. Saxonov identified various shortcomings in then-known multiplexing techniques, such as “instruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels,” and “increasing the number of distinguishable dyes is expensive and becomes impractical beyond a certain number.” *Id.*, ¶6.

56. Saxonov tried solving this problem using a “common or shared channel (‘the same optical channel’)” to detect signals from “reporters for two or more distinct targets.” *Id.*, ¶19. For example, in FIG. 3 (reproduced below), Saxonov illustrates target sequences 80, 82; probes 84, 86 with oligonucleotides 88, 90; and fluorophores 92, 94; when oligonucleotide 88 hybridizes to sequence

80 or oligonucleotide 90 hybridizes to sequence 82, the respective fluorophores separate from quenchers 96 and fluoresce. EX1004(Saxonov), ¶¶48-52, FIG. 3.

Fig. 3



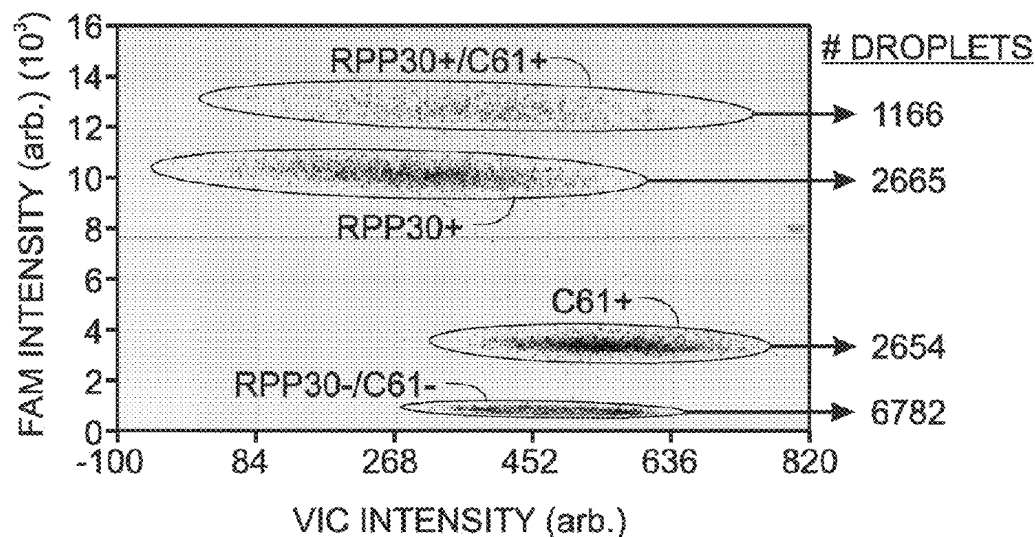
57. Saxonov describes different ways to distinguish the fluorophores' signals based on intensity, including that “one probe may be labeled with a different number of fluorophores than the other probe,” or “there may be more or less of one probe than the other in the sample,” or “the fluorophores themselves might be different, with one more or less intrinsically fluorescent than the other.” EX1004(Saxonov), ¶51. According to Saxonov, the “signal detected from each partition, and the partition itself, may be classified as being positive or negative for each of the reactions/targets contributing to the signal.” *Id.*, ¶41.

58. Saxonov states “[t]he data including all permutations of positives will generally fall into 2^N populations or clusters, where N is the number of targets, assuming that each population is distinguishable.” EX1004(Saxonov), ¶41.

59. FIG. 5 of Saxonov is part of an example which Saxonov describes as “a first exemplary digital PCR assay, in which multiplexing in a single channel is used to access copy number of the C61 gene... signals from two probes, one for

the gene of interest, C61, and one for a reference probe, RPP30, are collected together, as a single signal[.]” EX1004(Saxonov), ¶60. FIG. 5 illustrates clusters for the C61 and RPP30 genes in a common channel (the FAM channel, where FAM is a type of fluorophore).

Fig. 5

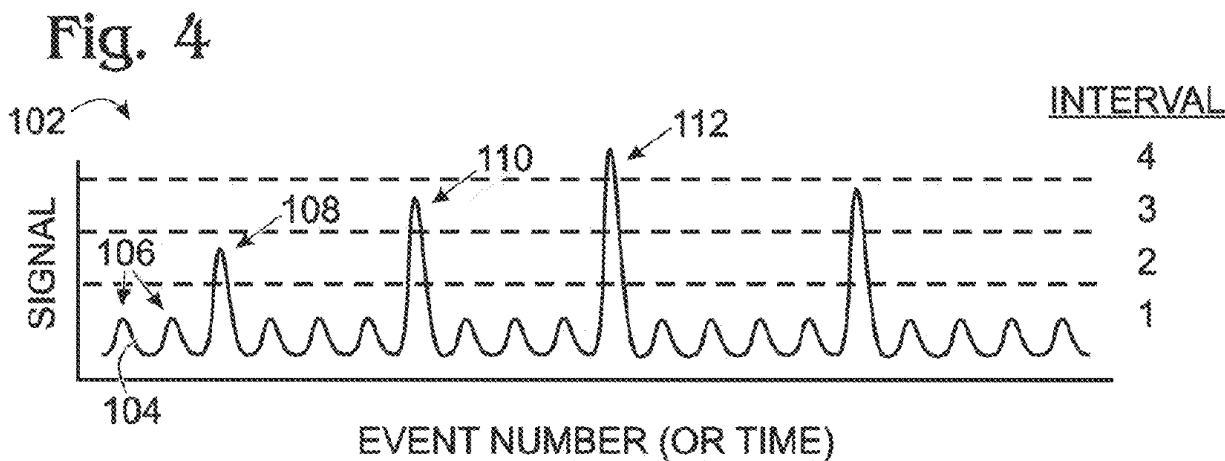


60. In FIG. 5, the RPP30-/C61- cluster of 6782 droplets “corresponds to droplets that are negative for RPP30 and C61 (i.e., droplets that did not include either gene).” EX1004(Saxonov), ¶64. The C61+ cluster of 2654 droplets “corresponds to droplets that are positive for C61 and negative for RPP30 (i.e., droplets that included the C61 gene but did not include the RPP30 gene).” *Id.*, ¶65. The RPP30+ cluster of 2665 droplets “corresponds to droplets that are positive for RPP30 and negative for C61 (i.e., droplets that included the RPP30 gene but did not include the C61 gene).” *Id.*, ¶66. The RPP30+/C61+ cluster of 1166 droplets

“corresponds to droplets that are positive for both RPP30 and C61 (i.e., droplets that included both genes).” *Id.*, ¶67.

61. FIG. 5 of Saxonov is consistent with Saxonov’s digital assays description above and with the “limiting dilution” regime (*supra* §V.A.): 6782 droplets were empty (the majority); 2654+2665=5319 droplets contained a single analyte (fewer than the number of empty droplets); and 1166 droplets contained both analytes (fewer than the number containing a single analyte).

62. This is also consistent with FIG. 4 of Saxonov, reproduced below, which according to Saxonov shows that peaks 106 “correspond to droplets containing no Target,” peaks 108 “correspond to droplets containing Target 1 but not containing Target 2 (T1+/T2-),” peaks 110 “correspond to droplets containing Target 2 but not containing Target 1 (T1-/T2+),” and peaks 112 “correspond to droplets containing both Targets 1 and 2 (T1+/T2+).” EX1004(Saxonov), ¶¶53-57. From FIG. 4, it may be seen that most droplets are empty (peaks 106), with fewer droplets containing one analyte (peaks 108 or 110), and even fewer droplets containing two analytes (peak 112). *Id.*, FIG. 4.



63. Saxonov’s FIG. 5 is fairly simple because there are only two analytes and four populations or clusters. According to Saxonov, as the number of targets (N) increases, the number of clusters increases as 2^N . EX1004(Saxonov), ¶41. Using the tables below, Saxonov shows a single target A (N=1) yields two clusters ($2^1=2$), two targets A and B (N=2) yield four clusters ($2^2=4$), and three targets A, B, and C (N=3) yields eight clusters ($2^3=8$). EX1004(Saxonov), ¶41.

	Target A	Intensity
Population 2	+	Highest
Population 1	–	Lowest

	Target A	Target B	Intensity
Population 4	+	+	Highest
Population 3	+	–	Intermediate
Population 2	–	+	Intermediate
Population 1	–	–	Lowest

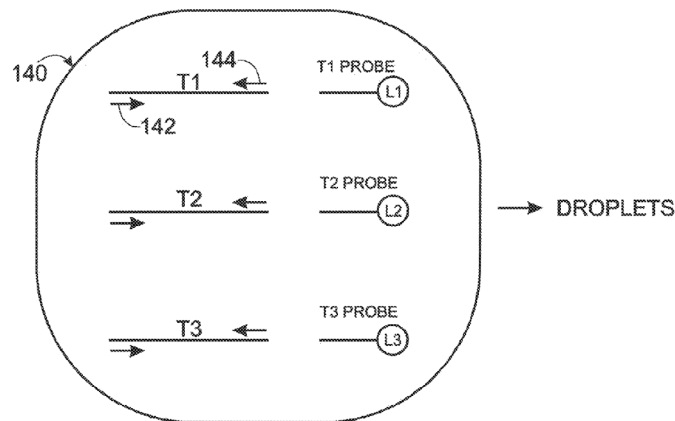
	Target A	Target B	Target C	Intensity
Population 8	+	+	+	Highest
Population 7	+	+	–	Intermediate
Population 6	+	–	+	Intermediate
Population 5	–	+	+	Intermediate
Population 4	+	–	–	Intermediate
Population 3	–	+	–	Intermediate
Population 2	–	–	+	Intermediate
Population 1	–	–	–	Lowest

64. As explained previously, Saxonov’s FIGS. 9 and 10 and ¶¶17, 18, and 76-79 were not carried forward from the Saxonov Provisional and thus it is my opinion, and my analysis assumes, that the subject matter disclosed by FIGS. 9 and 10 and ¶¶17, 18, and 76-79 is not prior art to the ’170 Patent. *See* §V.D. Nonetheless, Petitioner relies on this subject matter, and therefore, I briefly discuss it below.

65. According to Saxonov, FIG. 9 (reproduced below) is:

a schematic representation of an exemplary bulk phase mixture being separated into droplets during performance of an exemplary digital assay with multiplexed detection of three or more distinct targets (T1, T2, and T3) using a reporter for each target (a T1 probe, a T2 probe, and a T3 probe) each including a different luminophore (L1, L2, and L3, respectively)[.]

Fig. 9



EX1004(Saxonov), ¶17, FIG. 9.

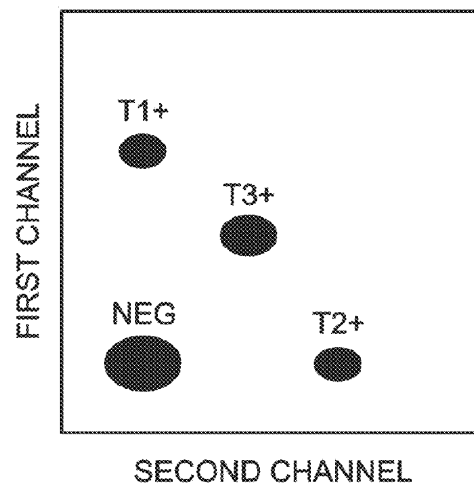
66. FIG. 9 shows that the volume containing the three targets T1, T2, T3 and corresponding probes is divided into droplets.

67. According to Saxonov, FIG. 10 (reproduced below):

is a schematic representation of an exemplary graph showing droplet (or peak) intensities for a T1/T2/T3 droplet assay that may be performed with the droplets of FIG. 9, where data from the T1, T2, and T3 probes are collected in a first optical channel and a second optical

channel and plotted as a function of intensity in the first channel (vertical axis) versus intensity in the second channel (horizontal axis), with intensities produced by exemplary populations or clusters of negative (NEG), T1-positive (T1+), T2-positive (T2+), and T3-positive (T3+) droplets represented by filled ellipses[.]

Fig. 10



EX1004(Saxonov), ¶18, FIG. 10.

68. Note that FIG. 10 does not include double-positive (e.g., T1+/T2+) or triple-positive (T1+/T2+/T3+) clusters, but instead shows just single-analyte clusters (either T1+, or T2+, or T3+). Saxonov states that in FIG. 10, “[t]o simplify the presentation, double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-positive population are *not shown*,” but alleges that “the populations containing more than one target may be resolved and distinguishable

from one another and from the single-target populations and the negative population.” EX1004(Saxonov), ¶¶78-79.¹

F. Overview of Silverbrook

69. U.S. Patent Application Publication No. 2011/0312704 to Silverbrook et al. (“Silverbrook”) was filed on June 1, 2011, and issued on December 22, 2011. EX1009(Silverbrook), §§(22), (43). Silverbrook discloses “a fluorescence-based detection technique to identify target molecules.” *See, e.g., id.*, ¶195. A test module using fluorescence-based detection is controlled by a test module reader, which may be a computer. *Id.*, ¶¶198, 200-201, FIGS. 1, 3, 96, 98. The data generated by the module can also be updated using the test module reader and network. *Id.* Silverbrook is silent as to detecting any unique combination of presence or absence of at least five polynucleotide analytes.

G. Overview of Maltezos

70. U.S. Patent Application Publication 2008/0003649 to Maltezos et al. (“Maltezos”) was filed on May 17, 2007, and issued on January 3, 2008. EX1010(Maltezos), §§(22), (43). Maltezos discloses a method of performing PCR in a thermal cycler, where the thermal cycler is controlled by a digital computer. *See, e.g., id.*, ¶¶7-8, 11-14, 18, 22, 28-29, 31, 34, 42, 132, 146-147, 166-167, 196,

¹ Emphasis added throughout except where noted.

212-214. Maltezos is silent as to detecting any unique combination of presence or absence of at least five polynucleotide analytes.

H. Overview of Oh

71. U.S. Patent Application Publication 2010/0311070 to Oh et al. (“Oh”) was filed on July 26, 2010, and issued on December 9, 2010. EX1011(Oh), §§(22), (43). Oh discloses “PCR modules with a combined PCR thermal cycle and PCR product detector” to improve on the then-existing limitations on “performing PCR using different samples at different temperature conditions.” *See, e.g., id.*, ¶¶3, 10, 61, 66-76, 86-105, FIGS. 1A-3. The PCR system utilizes a host computer. *Id.* While Oh discloses PCR modules, Oh is silent as to detecting any unique combination of presence or absence of at least five polynucleotide analytes.

I. Overview of Nakamura

72. U.S. Patent Application Publication No. US 2011/0160288 to Nakamura et al. (“Nakamura”) was filed on August 24, 2009, and issued on June 30, 2011. EX1025(Nakamura), §§(22), (43). Nakamura discloses “methods of screening for an agent for treating and/or preventing cancer.” *Id.*, ¶2, Abstract, ¶¶42-43, 46, 48. Nakamura is silent as to detecting any unique combination of presence or absence of at least five polynucleotide analytes.

J. Overview of Larson

73. U.S. Patent Application Publication No. US 2011/0250597 to Larson et al. (“Larson”) was filed on February 11, 2011, and issued on October 13, 2011. EX1017(Larson), §§(22), (43).

74. Larson discloses “droplet based digital PCR and methods for analyzing a target nucleic acid using the same.” EX1017(Larson), Abstract. Larson states that it is “based on the singular nature of amplifications at terminal or limiting dilution that arises because most often only a single target allele is ever present in any one droplet even when multiple primers/probes targeting different alleles are present.” *Id.*, ¶¶45, 98, 99. That is, that the samples are sufficiently diluted that a single target allele (target genetic sequence) is located within a droplet.

75. Larson describes terminal dilution as “the vast majority of reactions contain either one or zero target DNA molecules for practical intents and purposes,” and limiting dilution as “some reactions contain zero DNA molecules, some reactions contain one molecule, and frequently some other reactions contain multiple molecules, following the Poisson distribution.” EX1017(Larson), ¶6.

76. Larson asserts various advantages of having one allele per droplet:

Having ***only one*** haploid genome (i.e., one allele) per droplet gives droplet PCR advantages over standard singleplex or multiplex PCR in tubes or microwells. For

example, in traditional PCR, both alleles are present in the reaction mix so if there is a difference in the PCR efficiency between alleles, the allele with the highest efficiency will be over represented. Additionally, there can be variances in the sequence to which the PCR primers hybridize, despite careful primer design. A variance in the primer hybridization sequence can cause that primer to have a lower efficiency for hybridization for the allele that has the variance compared to the allele that has the wild type sequence. This can also cause one allele to be amplified preferentially over the other allele if both alleles are present in the same reaction mix.

These issues are avoided in droplet based PCR because there is only one template molecule per droplet, and thus one allele per droplet. Thus, even if primer variance exists that reduces the PCR efficiency for one allele, there is no competition between alleles because the alleles are separated and thus uniformly amplified.

EX1017(Larson), ¶¶99-100.

77. Larson discloses digital PCR (dPCR) assays for detecting different numbers of analytes. For example, FIG. 15 (reproduced below) discloses a “9-plex dPCR assay for spinal muscular atrophy with only two fluorophores, showing the process of optimizing droplet intensities.” EX1017(Larson), ¶35, FIG. 15.

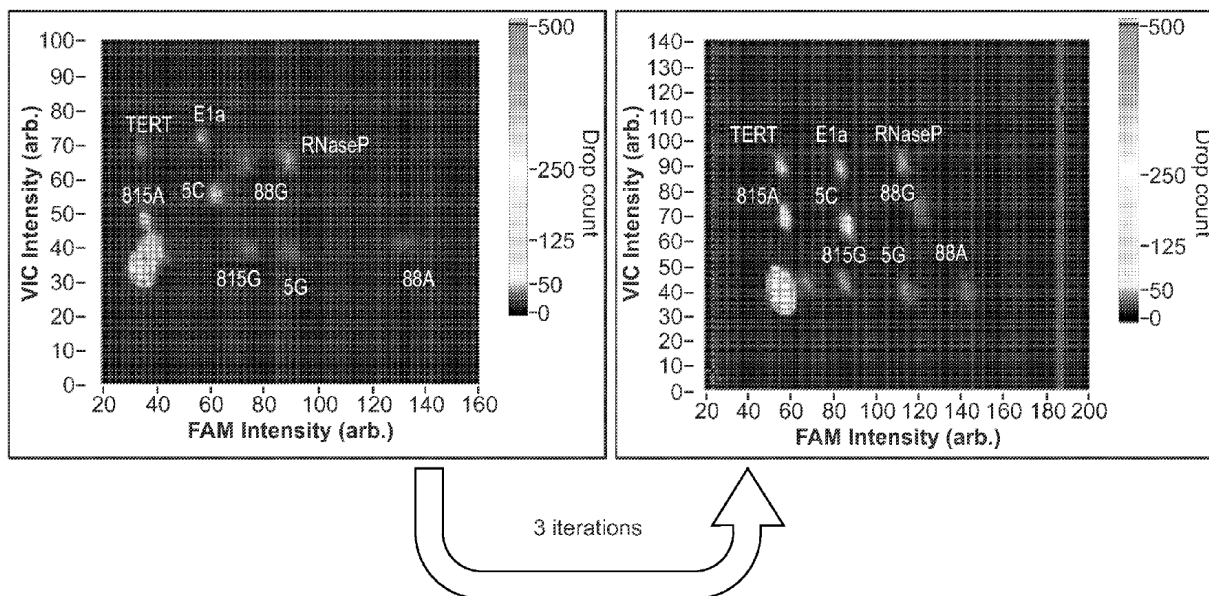


FIG. 15

78. Like Saxonov’s FIG. 10, Larson’s FIG. 15 shows only single-analyte clusters (respectively, TERT, 815A, E1a, 5C, 815G, RNaseP, 88G, 5G, 88A). EX1017(Larson), ¶35, FIG. 15.

79. Larson teaches “[h]igher degrees of multiplexing would require greater dilution,” because of the possibility for unintended “cross-reactivity” between analytes in a given droplet. EX1017, ¶129. Larson describes the

possibility for unintended “cross-reactivity” between analytes in a given droplet as follows:

A multiplexed (sic) assay can require a more dilute sample. For instance, at 10% occupancy a duplex reaction would have double occupancy 1% of the time. Hence 1 in 10 PCR+ droplets would be doubles, resulting in a final intensity at least as high and possibly higher than the brighter of the two probes. For a simple duplex system the contribution from each probe could be recovered. In this example the total number of PCR+ droplets for probe 1 would be (Probe1)+(Probe1+Probe2). Higher degrees of multiplexing would require greater dilution. For example, for a 4-plex at 1% occupancy the probability of one probe overlapping any of the other 3 is ~3%, and that error may be too high for some applications. The need for large dilutions strongly favors the large number of dPCR reactions.

EX1017(Larson), ¶129.

80. According to the excerpt above, Larson teaches increasing the sample dilution as the number of analytes increases, in order to reduce the probability that any droplet contains even two analytes, let alone more than two.

81. Larson uses the term “occupancy” to describe the number of analytes in droplets:

In a serial dilution the average number of target DNA molecules per droplet—called the “occupancy” from this point forward—should decrease in direct proportion to the DNA concentration. The occupancy was calculated from Poisson statistics using the following equation well known to those experienced in the art:

$$\text{occupancy} = \ln\left(\frac{P + N}{N}\right),$$

where P and N are the numbers of PCR(+) and PCR(−) droplets respectively.

EX1017(Larson), ¶96.

82. According to Larson’s apparent definition of “occupancy,” the term “10% occupancy” refers to a dilution at which 90% of droplets are empty, 10% of droplets contain analyte, and 10% of the droplets that are not empty (that is, 1% of all the droplets) droplets contain exactly two analytes. In this situation, Larson teaches that in a duplex system (an assay for two analytes), the contribution from each probe can be recovered from a droplet that contains both of the analytes.

83. But for “higher degrees of multiplexing,” that is, more than two analytes, Larson teaches that “greater dilution” is needed. *Id.*, ¶129. Larson gives the example of a “4-plex” (four analyte assay) at a “1% occupancy,” referring to a dilution at which 99% of droplets are empty and 1% of droplets contain an analyte. *Id.*, ¶129. Even at this high dilution, Larson states that the “probability of one

probe overlapping any of the other 3” may be “too high for some applications,” so the “need for large dilutions strongly favors the large number of dPCR reactions.” EX1017(Larson), ¶129.

84. Accordingly, Larson expressly teaches to increase the sample dilution as the number of analytes increases, in order to reduce the probability that one probe overlaps any of the other probes – that is, to reduce the probability that any droplet contains even two analytes, let alone more than two.

VI. CLAIM CONSTRUCTION

85. For purposes of this declaration, I have reviewed the challenged claims of the ’170 Patent in view of their common and ordinary usage and in view of the specification of the ’170 Patent.

86. I understand that Patent Owner’s construction of some claim terms differs from that of Petitioner. My analysis below is based on, and consistent with, Patent Owner’s proposed claim constructions set forth at EX1003. For example, I understand that Patent Owner proposes that terms such as “each [of the at least five] hybridization probe[s],” and the “exciting” step should be interpreted in accordance with their plain and ordinary meaning. EX1003, 11-13, 21-23; EX2011, 14-15, 16-17, 22-25; EX2012, 16-18. For the term “cumulative signal measurement,” I understand the Patent Owner has taken the position that this term should be construed as meaning “[m]easurement of the cumulative signal intensity

signal(s) in the plurality of droplets.” EX1003, 16-18; EX2011, 19-21. This is consistent with the term’s plain and ordinary meaning, and Petitioner conceded as such. EX2012, 15-16.

87. I agree with the Patent Owner’s positions because these positions are consistent with the common an ordinary usage of the terms, and in particular how those terms are used the ’170 Patent specification, based on my own understanding as at least a POSA. However, my ultimate opinion that the references cited in the Petition do not teach the challenged claims of the ’170 Patent would remain the same even under the Petitioner’s proposed constructions.

VII. GROUNDS OF CHALLENGE

88. Petitioner points primarily to Saxonov as rendering the ’170 Patent claims obvious, either alone or in view of Nakamura, Larson, Silverbrook, Maltezos and/or Oh. However, for the reasons set forth below, it is my opinion that none of these references, whether alone or in combination, teach the challenged claims of the ’170 Patent.

A. Ground 1 (Claims 1-9, 20): Obviousness over Saxonov

1. Challenged Claims and Saxonov Differ in Kind

89. While the ’170 Patent and Saxonov both aim to extend the number of analytes that can be examined simultaneously, they solve these problems in significantly different ways.

90. For example, Saxonov uses the “same optical channel” to detect different analytes, ostensibly to reduce the cost of additional optical channels and optical dyes. *See, e.g.*, EX1004, Title, Abstract, ¶6 (“[I]nstruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels. Also, increasing the number of distinguishable dyes is expensive and becomes impractical beyond a certain number.”), ¶¶7-9 (“The present disclosure provides a system...for performing a digital assay with multiplexed detection of two or more distinct targets in the same optical channel.”), ¶¶11, 19, 41, 47-75 (describing examples of digital PCR assays, in which multiplexing in a single channel is used to detect different genes).

91. To detect different analytes, Saxonov extensively dilutes the sample into numerous droplets such that most of the droplets are empty (contain zero analyte), and the next largest population of droplets contains a single analyte. *See, e.g., id.*, ¶3 (“In an exemplary digital assay, a sample is separated into a set of partitions, generally of equal volume, with each containing, on average, less than about one copy of the analyte.”); *supra* §V.A. Droplets with zero analyte (the majority of droplets) provide no information, but inevitably arise by the procedure. *Id.*; *supra* §V.A. This reduces the number of analytes in a droplet, making it easier to identify the analytes, with the easiest case being that of a single analyte per

droplet. Indeed, Saxonov is replete with examples of how to identify a *single* analyte within a droplet. *See, e.g.*, EX1004, ¶¶47-75.

92. For detecting multiple analytes in the same optical channel, droplets with a single analyte are key to Saxonov’s method. For example, each of the droplets will contain either a “high” intensity probe corresponding to a first analyte, or a “low” intensity probe corresponding to a second analyte—but not both simultaneously—allowing two analytes to be examined in the same optical channel. *Supra*, ¶57. Because of the Poisson distribution, it is inevitable that some droplets will contain two analyte molecules, or even more than two (with frequency dropping quickly as the number of molecules/droplets increases). *Supra*, ¶33. Such multi-analyte droplets are unnecessary in Saxonov’s method for obtaining the desired results, because the single-molecule droplets unambiguously provide the desired data of whether individual analytes are present or absent in the sample.

93. Saxonov’s approach has a number of disadvantages. For example, it requires many droplets and thus many PCR reactions, the majority of which provide no information (because the droplets are empty). *Supra*, ¶¶61-62. Aside from wasting reagents, this is cumbersome to perform and get the optical readouts, because each droplet has to be assessed. As a consequence, empty droplets reduce the number of samples that can be analyzed in a given period of time, and the

amount of information that can be gathered during that time. Additionally, diluting down to a single analyte is complicated by the possibility that different analytes in the sample may be present at very different concentrations than each other, and this is not known before performing the dilution, or the assays. Thus, the optimal dilution for analyte A in the sample can be very different from the optimal dilution for analyte B in the same sample. This requires a very broad dilution series, meaning the vast majority of drops are uninformative, *e.g.*, contain either no molecules or too many molecules.

94. The '170 Patent solves the problem of detecting different analytes in a sample by measuring cumulative optical signals using a coding scheme. According to embodiments of the '170 Patent's method, PCR reactions go to completion such that all the original colorimetric probe molecules (whose fluorophores are quenched) are hybridized, thereby liberating the colorimetric signal. For example, if two probes that are read in the same optical channel have 1000 units of fluorescence for analyte A and 500 units of fluorescence for analyte B, then one can distinguish between 500, 1000, and 1500 units in that channel and hence determine whether the sample contains A, B, or both A and B analytes. Similarly, with appropriate choices of fluorescence units for probes with multiple colors, one can make the same distinction between different analytes.

95. An important feature taught by the '170 Patent is how to choose probe colors and intensities that uniquely determine a given analyte, even if that analyte is mixed with other analytes at the same time. This avoids the degeneracy problem, which arises when the same intensity values are consistent for two different combinations of analytes. For example, if intensity values 1, 2, 4, 8, 16, 32 are chosen for probes read in the same optical channel, every combination of present/absent analytes is unique. This method of decoding cumulative signals is different in kind (not just degree) from Saxonov, and makes it much easier to analyze multiplexed samples.

96. Claim 1 of the '170 Patent, reproduced above in §V.B., is directed to “unambiguously detecting any unique combination of presence or absence of *at least five polynucleotide analytes* in a plurality of droplets.” EX1001, 65:30-33. A sample comprising, or potentially comprising, at least one of these analytes is mixed with “*at least five hybridization probes*,” each comprising “at least one fluorophore and at most four fluorophores.” EX1001, 65:37-40. The sample is partitioned into said plurality of droplets. EX1001, 65:41. If one or more of the polynucleotide analytes is present in the plurality of droplets, one or more signals are generated that “comprise at least one signal generated by excitement of said at least one fluorophore[.]” EX1001, 65:42-47. Claim 1 recites measuring the one or more signals to generate cumulative intensity measurement that “corresponds to

the presence of a unique combination of presence or absence of said at least five polynucleotide analytes in said sample,” and “determining whether each of said at least five polynucleotide analytes is present, in any unique combination of presence or absence, based on said cumulative intensity measurement.” EX1001, 65:48-61. While few droplets may contain all five analytes, the power of the ’170 Patent lies in its flexibility to detect any possible combination of the analytes within the sample, in a manner that each analyte may be uniquely distinguished from each other analyte. *Supra* §V.B. At the time of the ’170 Patent and its priority applications, no such solution was available to solve the problem of how to increase the number of analytes which could be non-degenerately detected in a sample. *Supra* §V.B.; *See also* EX1001, 1:31-43 (“There is a need for multiplexed reactions that can be carried out in a single solution.”)

2. Saxonov Does Not Teach How to Identify Three or More Analytes Within a Droplet

97. As described above at ¶90, droplets containing more than one analyte were unnecessary in Saxonov’s method for obtaining the desired results, because the single-molecule droplets unambiguously provided the desired information about whether individual analytes are present or absent in the sample.

98. To the extent that Saxonov contemplates identifying three or more analytes a given droplet, Saxonov falls far short of describing how to actually do

so. This is because Saxonov had no need to try to solve that problem: the single-analyte droplets yielded the information that Saxonov apparently sought—an identification of whether an analyte was present in the sample. Saxonov did not contemplate the solution provided by the '170 Patent, because there was no need in Saxonov to even contemplate the possibility of a large number of analytes per droplet—Saxonov’s limiting dilution avoided this issue—let alone solve the problem of how to non-degenerately identify that many analytes.

99. Saxonov fails to teach how to non-degenerately distinguish even *three* analytes in a droplet, let alone more (*e.g.*, at least five). Illustratively, Saxonov provides the following table purporting to describe the “Intensity” of each of eight ($2^{N=3}$) clusters for three analytes in a single channel:

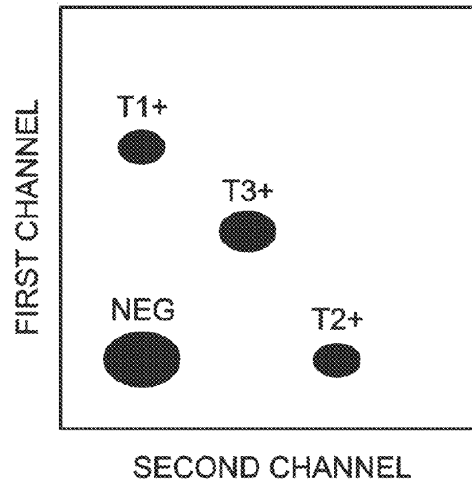
	Target A	Target B	Target C	Intensity
Population 8	+	+	+	Highest
Population 7	+	+	–	Intermediate
Population 6	+	–	+	Intermediate
Population 5	–	+	+	Intermediate
Population 4	+	–	–	Intermediate
Population 3	–	+	–	Intermediate
Population 2	–	–	+	Intermediate
Population 1	–	–	–	Lowest

100. However, Saxonov does not explain how this many intensities might be measurably *distinguished* from one another using a single channel.

Specifically, Saxonov does not explain the differences (if any) amongst the various “[i]ntermediate” intensities, nor whether such intensities are non-degenerate, nor how such differences (if any) might be detected using just a single channel. Rather than explaining *how* to design the probes such that all of the intensities are *non-degenerate*, Saxonov merely “*assum*[es] that each population is distinguishable.” EX1004(Saxonov), ¶41.

101. As another example, although it is my understanding that Saxonov’s FIG. 10 and ¶¶77-79 are not prior art to the ’170 Patent (*see* §V.D.), these portions highlight Saxonov’s deficient teachings in how to obtain meaningful information, even from double-positive and triple-positive droplets. Saxonov states that double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-positive population (T1+/T2+/T3+) in FIG. 10 are not shown “[t]o simplify the presentation” but “may be resolved and distinguishable from one another and from the single-target populations and the negative population.” EX1004(Saxonov), ¶¶78-79. Yet, Saxonov does not actually explain *how* populations of droplets that contain three or more analytes (let alone at least *five* analytes) might actually be “resolved and distinguishable from one another” – let alone in the specific manner recited in claim 1. EX1004, ¶¶78-79.

Fig. 10



102. Saxonov’s ¶20 further confirms that Saxonov did not really know, or teach, how to distinguish clusters—whether in one channel or multiple channels:

“[t]hree targets, two in a first channel and one in a second channel, would again generate eight clusters or populations of data, but they would be separated in a two-dimensional intensity space *and so in principle more easily resolvable*.”

EX1004(Saxonov), ¶20. This falls far short of teaching a POSA that the clusters are *actually* resolvable, let alone how to design the probes such that the clusters not only are resolvable but are *non-degenerate*.

3. Petitioner’s Proposed Saxonov Scheme Contradicts Saxonov’s Own Teachings

103. Petitioner and its proffered expert, Dr. Carl Batt, use Saxonov’s teachings (many of which are not prior art based on my understanding, *supra*

§V.D.), as a jumping-off point to propose two different probe schemes which would allegedly be obvious to detect eight or nine analytes in the manner recited in claim 1 (which recites at least “five” analytes). Note that these schemes do not actually appear in Saxonov.

104. The first proposed scheme, reproduced below, is for three colors and three intensities per color, which according to Petitioner “would allow the non-degenerate identification of *nine* different analytes.” Petition at 30 (emphasis in original); EX1002(Batt Decl.), ¶151.

	Color 1	Color 2	Color 3
Intensity 1	Analyte 1	Analyte 4	Analyte 7
Intensity 2	Analyte 2	Analyte 5	Analyte 8
Intensity 3	Analyte 3	Analyte 6	Analyte 9

105. According to Petitioner, in the second proposed scheme, reproduced below, using four colors and two intensities per color, “*eight* analytes can be unambiguously detected.” Petition at 31 (emphasis in original); EX1002(Batt Decl.), ¶153.

	Color 1	Color 2	Color 3	Color 4
Intensity 1	Analyte 1	Analyte 3	Analyte 5	Analyte 7
Intensity 2	Analyte 2	Analyte 4	Analyte 6	Analyte 8

106. Petitioner asserts that “both schemes described—three colors at three intensities and four colors at two intensities—allow for the analysis of samples that have at least five analytes and a POSA would have reasonably expected success in using either scheme that is contemplated in Saxonov.” Petition at 31-32; EX1002(Batt Decl.), ¶¶154-156.

107. Indeed, Petitioner’s schemes so vastly oversimplify and mischaracterize Saxonov’s disclosure that they contradict Saxonov’s own teachings. More specifically, Petitioner’s proposed eight- and nine-analyte schemes include intensities and colors only for *single-analyte* droplets; this is clearly reflected in each of their boxes containing only *one* analyte (e.g., “Analyte 1,” “Analyte 2,” etc.). Petition at 30-31. Petitioner’s proposed schemes do *not*

represent any droplets containing *two* analytes (e.g., do not include boxes containing Analyte1+Analyte2 or Analyte3+Analyte8), nor containing *three* analytes (e.g., do not include a box containing Analyte 4+Analyte6+Analyte8), let alone containing *more than three* analytes. Petition at 30-31.

108. This is contrary to Saxonov’s express teaching that “data including all permutations of positives will generally fall into 2^N populations or clusters, where N is the number of targets, assuming that each population is distinguishable.” EX1004, ¶41. Furthermore, a POSA would have understood that there would be N number of single analyte droplets and (2^N minus N) number of multi-analyte droplets. From this teaching, a POSA would have understood Saxonov to teach N=8 analytes yields 256 clusters ($2^8=256$), eight for single-analyte droplets and **248** (256 minus 8) for multi-analyte droplets. Additionally, a POSA would have understood Saxonov to teach N=9 analytes yields 512 clusters ($2^9=512$), nine for single-analyte droplets and **503** (512 minus 9) for multi-analyte droplets. While Saxonov “[a]ssum[es]” that clusters are distinguishable, Saxonov certainly does not teach how to distinguish among the hundreds of clusters that the Petitioner’s proposed schemes should have included, had they comported with Saxonov’s express teachings.

109. Petitioner does not attempt to represent even a subset (let alone all) of the **248** multi-analyte droplets in the eight-analyte scheme; nor even a subset (let

alone all) of the **503** multi-analyte droplets in the nine-analyte scheme. As such, in my opinion, Petitioner’s oversimplified representations ignore Saxonov’s express teachings about the number of clusters their purported schemes would actually produce. If Petitioner were to argue that they omitted the multi-analyte droplets from their representations for simplicity, this would merely mirror Saxonov’s own deficiencies regarding multi-analyte droplets (*e.g.*, Saxonov’s deficient teachings regarding **how** to distinguish and correctly interpret clusters from one another that came from droplets containing different **combinations** of multiple analytes than one another, especially for **more than three analytes and/or more than one color**, let alone five analytes and four colors, as recited in claim 1). *Supra* §§V.E., VII.A.1-2.

110. I must note that Petitioner’s schemes are so vastly oversimplified that they omit that which Saxonov allegedly renders obvious. Specifically, claim 1 of the ’170 Patent recites “determining whether each of said [at] least five polynucleotide analytes is present, in any unique combination of presence or absence, based on said cumulative intensity measurement.” EX1001, 65:55-58. As noted above in §§VII.A.1-2., Petitioner’s proposed eight- and nine-analyte schemes include intensities and colors only for **single-analyte** droplets, omitting any droplets containing **two, three, or more than three** analytes, and certainly not representing “**any** unique combination of presence or absence” of at least **five**

polynucleotide analytes. Petition at 30-31. Petitioner’s failure even to represent this key claim feature in their purported eight- and nine-analyte schemes speaks volumes about how far their strained interpretation of Saxonov falls short of teaching all that is recited in claim 1.

B. Ground 2 (Claims 10-12): Obviousness Over Saxonov and Nakamura

111. The Petition alleges that claims 10-12 of the ’170 Patent are obvious over Saxonov in view of Nakamura. Petition at 50-52. Claims 10-12 depend on and add limitations to claim 1. The Petitioner argues that Nakamura teaches “performing PCR assays on a ‘tumor-specific’ basis” (claim 10), using “biological samples derived from a subject” (claim 11), and “the polynucleotide analyte may indicate the presence of cancer or ‘indicates that the subject suffers from or is at risk of developing lung and/or esophageal cancer’” (claim 12). *Id.*, 50-52. Even assuming that Nakamura teaches that for which it is cited, such features do not cure the many deficiencies of Saxonov as detailed elsewhere herein. *See supra* §§V.I., VII.A.

C. Ground 3 (Claims 13-16): Obvious Over Saxonov and Silverbrook

112. The Petition alleges that claims 13-16 are obvious over Saxonov in view of Silverbrook. Petition at 52-54. Claims 13-16 depend on and add limitations to claim 1. The Petitioner argues that Silverbrook teaches “transmitting

test results through a computer network” (claim 13), “molecular diagnostics where treatment options may differ depending on pathogen load” and facilitating “clinical management decisions such as infection control and antibiotic use” (claims 14 and 15), and “detecting various infectious diseases and forms of cancer” (claim 16).

Id., 52-54. Even assuming that Silverbrook teaches that for which it is cited, such features do not cure the many deficiencies of Saxonov as detailed elsewhere herein. *See supra* §§ V.F., VII.A.

D. Ground 4 (Claims 17, 19): Obviousness Over Saxonov and Maltezos

113. The Petition alleges that claims 17 and 19 of the ’170 Patent are obvious over Saxonov in view of Maltezos. Petition at 55-57. The Petitioner relies on Maltezos as allegedly teaching “[a] computer perform[ing] the detecting and/or measuring step.” *Id.* Even assuming that Maltezos teaches that for which it is cited, such features do not cure the many deficiencies of Saxonov as detailed elsewhere herein. *See supra* §§ V.G., VII.A.

E. Ground 5 (Claim 18): Obviousness Over Saxonov, Maltezos, and Further in View of Oh

114. The Petition alleges that claim 18 of the ’170 Patent is obvious over Saxonov in view of Maltezos and Oh. Petition at 57-58. The Petitioner’s remarks regarding Maltezos are addressed in §VII.D. The Petitioner argues that

“[i]nformed by Saxonov and Oh, a POSA would have found it obvious to use a remote computer to perform the measuring (and calculating) step.” Petition at 58. Even assuming that Oh teaches that for which it is cited, such features do not cure the many deficiencies of Saxonov as detailed elsewhere herein. *See supra* §§V.H., VII.A., VII.D.

F. Ground 6 (Claims 1-9, 20): Obviousness Over Saxonov and Larson

115. Saxonov and/or Larson, either alone or in combination, fail to disclose or teach claims 1-9 and 20 of the '170 Patent.

1. Saxonov Is Deficient

116. As discussed previously (*supra* §VII.A.), it is my opinion that Saxonov fails to teach limitations of claims 1-9 and 20. In Ground 6, Petitioner heavily relies on FIG. 10 and ¶¶17, 18, and 76-79 of Saxonov—the very sections which are not carried over from the Saxonov Provisional. *Supra* §§V.D., VII.A. For this reason, in addition to the reasons set forth further above regarding Saxonov’s many deficiencies, it is my opinion that Saxonov fails to teach the challenged claims of the '170 Patent.

2. Larson Is Deficient

117. Among other things, Petitioner falls short of explaining why a POSA would have found it obvious to try to combine Larson with Saxonov to determine

whether each of at least five polynucleotides is present, *in any unique combination of presence or absence*. The Petition points to Larson as teaching that “distinguishing nine targets with combinations of two colors and intensities, along with techniques for tuning the signal from each droplet:”

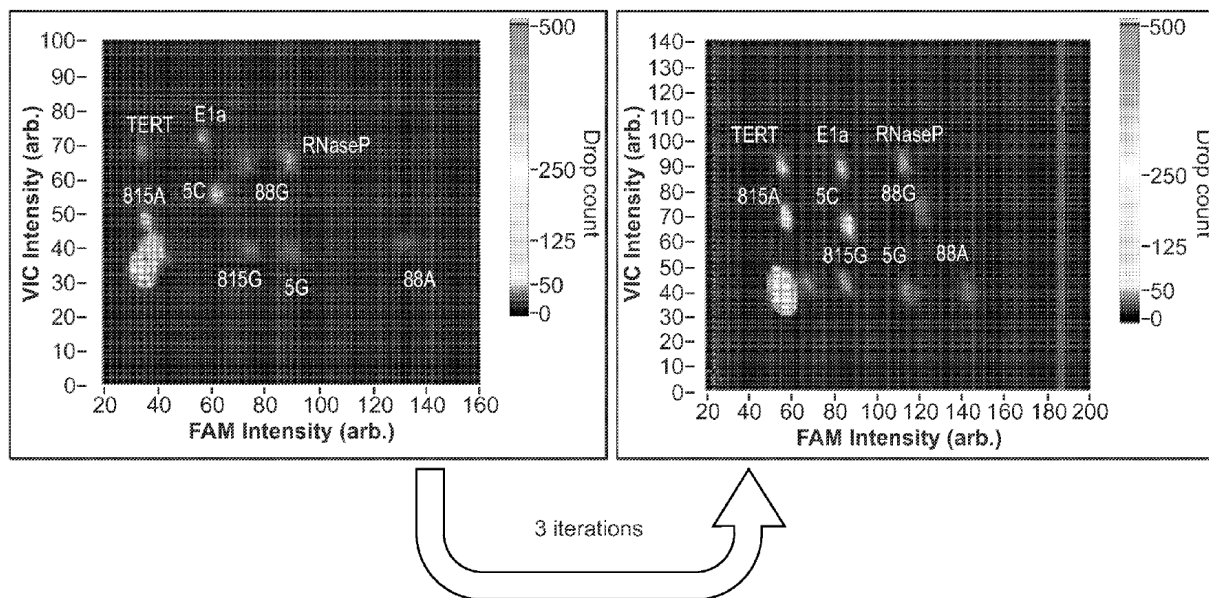


FIG. 15

Petition at 61-62 (citing EX1017(Larson), FIGS. 12, 15, ¶¶134-138, 150-151).

118. Like Saxonov’s FIG. 10, Larson’s FIG. 15 excludes double-positive clusters (here, TERT+/815A+, 5C+/815G+, or the like), triple-positive clusters (here, TERT+/815A+/E1a+, 88A+/815G+/RNaseP+, or the like). Instead, Larson’s FIG. 15 only includes *single*-analyte clusters (e.g., TERT, 815A, E1a, 5C, 815G, RNaseP, or 88G, 5G, 88A). EX1017(Larson), FIG. 15. The absence in Larson’s FIG. 15 of any double-, triple-, or even higher-multiple-positive clusters

indicates that the droplets Larson measured contained a *single* analyte. *Supra* §V.J.

119. Larson asserts that it is “compatible with all distributions of DNA loading that conform to limiting or terminal dilution.” EX1017(Larson), ¶¶52, 45, 74, 119-121. While such mention of limiting dilution would nominally appear to accommodate multiple analytes in a droplet, Larson otherwise expressly teaches *increasing* sample dilution as the number of analytes increases, to *reduce* the probability that one probe overlaps any of the other probes – that is, to reduce the probability that any droplet contains even two analytes, let alone more than two. *See supra* §V.J. That is, the absence in Larson’s FIG. 15 of any double-, triple-, or even higher-multiple-positive clusters indicate that the droplets Larson measured contained a *single* analyte, and this is consistent with Larson’s repeated teachings to use a single analyte per droplet. EX1017 (Larson), ¶¶99-100 (“These issues are avoided in droplet based PCR because there is only one template molecule per droplet, and thus one allele per droplet.”), ¶45. A POSA would not have found Larson’s teachings at all instructive on how determine whether each of at least five polynucleotides is present, *in any unique combination of presence or absence*. Indeed, Petitioner concedes “both references are based on the same approach (*i.e.*, droplets).” Petition at 61.

120. Therefore, it is my opinion that a POSA would not have found it obvious to try to combine Larson with Saxonov to determine whether each of at least five polynucleotides is present, *in any unique combination of presence or absence*.

G. Grounds 7-10 (Claims 10-19): Obviousness Over Saxonov and Larson and Further in View of Nakamura, Silverbrook, Maltezos, and/or Oh

121. Saxonov combined with Larson further in view of Nakamura (claims 10-12), Silverbrook (claims 13-16), Maltezos (claims 17 and 19), and Maltezos and Oh (claim 18) fail to disclose or teach claims 10-19 of the '170 Patent. Even assuming, purely for the sake of argument, that Nakamura, Silverbrook, Maltezos, and/or Oh teach that for which they are cited, such features do not cure the many deficiencies of Saxonov and Larson as detailed elsewhere herein. *Supra* §§VII.A-F.

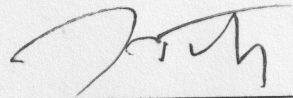
VIII. DECLARATION

122. This Declaration and my opinions herein are made to the best of my knowledge and understanding, and based on the material available to me, at the time of signing this Declaration. I declare under penalty of perjury under the laws of the United States that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true, and

further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 or Title 18 of the United States Code. I executed this Declaration at Weston, Massachusetts.

Dated: October 30, 2024

By



KEVIN STRUHL